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EXAMINER
YAEN, CHRISTOPHER H

ART UNIT	PAPER NUMBER
1642	18

DATE MAILED: 05/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/637,977	Applicant(s) MURRAY ET AL.	
	Examiner Christopher H Yaen	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,30 and 34-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,30 and 34-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8,9,17* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet* .

Continuation of Attachment(s) 6). Other: Notice to Comply with Sequence Rules.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of the sequence X83107, BMX non-receptor tyrosine kinase in Paper No. 16 is acknowledged. The traversal is on the ground(s) that the restriction to a single sequence is improper. This is not found persuasive because there are over 3500 nucleic acid sequence that need to be searched in the instant case. Applicant argues that it would not be undue burden for the examiner to search a representative number of sequences (i.e. ten sequence) that if found allowable would render all other sequences also allowable. However, in the instant case, there are approximately 3500 nucleotide sequences in the case that seem to be nucleotide sequences that encode separate and distinct proteins. Furthermore, the sequences claimed do not fall within the same genus of nucleotide sequences the encode a family of proteins that are related by function or structure. Because each protein is considered a separate invention and because the search for the approximately 3500 nucleotide sequence would constitute an unreasonable search and because the search for the different nucleotide sequences are not overlapping nor co-extensive, the requirement for restriction is deemed proper.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 8,30, and 34-37 are pending and examined on the record, to the extent the claims read on the elected nucleotide sequence of X83107, BMX non-receptor tyrosine kinase.

Information Disclosure Statement

3. The Information Disclosure Statements filed 5/17/2001, 8/30/2001, and 1/27/2003 (paper nos. 8,9, and 17) are acknowledged and considered. A signed copy of the IDS is attached hereto.

Specification

4. The disclosure is objected to because of the following informalities: the tables have to indicate the sequence identification numbers associated with each of the genes.

Appropriate correction is required.

5. The disclosure is objected to because of the following informalities: the priority data must be updated in the first paragraph of the specification.

Appropriate correction is required.

CRF- Sequence Compliance

6. The instant application is not fully compliant with the sequence rules. Each sequence claimed or cited in the instant application must be associated with a specific sequence identification number. It is noted that some of the sequences claimed in the different tables do not have accession numbers. Because the sequences or genes claimed in the tables are accession numbers and because the accession numbers are often updated, the genes claimed cannot be determined. In addition, the accession numbers enumerated in the tables do not allow the office to conduct an internal search of our patent databases for interference purposes. Therefore, in reply to this instant office action, applicant is required to amend the claims and specification so as to refer to each of the cited gene sequences with a specific sequence identification number.

Claim Rejections - 35 USC § 112, 2nd paragraph

7. Claims 8, 30, and 34-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. With regards to claims 8, 34, and 35 in the recitation of the phrase "one or more genes", it is unclear as to which other gene is being referred.

9. With regard to claims 8, 30, 34-37 in the recitation of the phrase "Table 1, Table 2, Table 3, Table 4, Table, 5", claims are not allowed to recite tables because such parts of the specification are subject to amendments. Applicant is required to remove references to "tables" and is advised to substitute specific elements of the table into the claims. Each sequence must be identified by a specific SEQ ID No:. It is noted that some of the so called genes have stated "no accession is listed". It is not clear how one of skill or the USPTO is to conduct a reasonable search. Furthermore, the SEQ ID No: for BMX itself is missing. A reasonable search cannot be conducted for the claimed method.

10. With regard to claims 8,30,34-37 in the recitation of the term "fragment", it is unclear as to which fragment is intended to be encompassed within the claims. Because the fragment intended in not adequately defined in the specification, the metes and bounds of the term cannot be determined.

11. With regard to claims 8, 34 and 35 in the recitation of the term "tissue type" it is unclear as to which type of tissue is being referred, does the applicant intend for skin to be included in the tissue type?

12. With regard to claims 8,34, and 35 in the recitation of the term "difference", it is unclear as to the intended difference sought. There is no way for the skilled artisan to determine what range is an acceptable difference. Is the difference intended to be a positive or negative "difference" (i.e. would an over or lack of expression indicate angiogenesis?)?

13. With regard to claims 30, 35 and 37 in the recitation of the term "angiogenesis modulator protein (AMP)", this is a laboratory name of which no know function or structure has been associated. Because this name is arbitrarily assigned, the metes and bounds of the term cannot be determined.

14. With regard to claims 30, 36 and 37 in the recitation of the term "high level", it is a relative term of which one of skill in the art cannot adequately determine because there is no control or base level from which to compare the normal levels with "high levels".

15. With regard to claims 34 and 36 in the recitation of the term "nucleic acid probe", it is unclear as to which probe is intended to be the used for the measurement. Because the sequence or probe has not been associated with a sequence identification number, one of skill in the art would not know the metes and bounds of the term.

16. With regards to claims 30, 36 and 37, it is unclear whether the determination being made is to use a protein or a nucleic acid probe. The recitation of "determining the level of an angiogenesis modulating protein (AMP)", could refer to either a protein or gene and therefore the claim is rendered indefinite. Correction is required.

17. Claims 8,30,34-37 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements and omitting essential steps, such

omission amounting to a gap between the elements and steps of the method. See MPEP § 2172.01. The omitted elements and steps are: how, what, and where the method of diagnosis is to take place, the specification has not defined any particular methodological steps and with what probes, or in what specific tissues the diagnosis is to take place. As such the method steps are considered vague and indefinite.

Claim Rejections - 35 USC § 112, 1st paragraph

18. Claims 8,30, 34-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of diagnosing angiogenesis comprising the determination of gene expression of a BMX gene, followed by comparing the BMX gene expression to the BMX gene in normal tissue or from a second patient. The art teaches that examination of human umbilical cord endothelial cells or HUVEC with a probe to BMX gene revealed a 2.7 kb band indicating that the gene is constitutively expressed in the absence of an angiogenic event (Oncogene 1994;9:3683-3688, IDS 32). The art also teaches that BMX (also known as etk) is activated upon TNF binding to the TNF receptor 2 (TNFR2) (Pan *et al* (Mol. Cell Biol. 2002 Nov;22(21):7512-7523). It is speculated by Pan *et al* that BMX and TNFR2 associate in a complex that is in the "closed" state, wherein TNF binding to the receptor triggers the complex to become

"open" thereby activating other downstream regulators that mediate angiogenesis (see figure 7, page 7522). The references combined suggest that BMX gene expression is not necessarily upregulated in angiogenic events but rather an alteration in protein structure would initiate angiogenesis. The instant specification prophetically discloses the desired embodiments of the instant invention wherein changes in the expression patterns of tissues in question when compared to normal tissues would indicate tissues that were undergoing angiogenesis. The working examples of the instant invention have only provided methodological steps or protocols for accomplishing hybridization techniques. One of skill in the art would not be enabled to practice the full scope of the instant invention because the determination of gene expression of BMX has not been correlated to the diagnosis of angiogenesis. The skilled artisan has not been taught the level of BMX expression that would indicate a predisposition to an angiogenic event. No comparisons of normal tissue versus tissue suspected of undergoing angiogenesis have been made so as to indicate that there would be a difference in expression levels.

Therefore, given the lack of knowledge as it pertains to the mechanism of BMX activation, the expression levels between tissue suspected of undergoing angiogenesis, and the lack of proper teachings in the specification so as to teach or guide the skilled artisan to practice the full scope of the invention, the skilled artisan would be forced into undue experimentation to determine the multiple unknown factors that are required in order the practice the instant invention.

Claim Rejections - 35 USC § 102

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

20. Claims 8, 30, 34 and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Tamagnone *et al* (Oncogene 1994;9:3683-3688, IDS 32). The claims are read to the extent that they read on the elected gene, BMX. Claims are drawn to a method comprising determining the expression of BMX using a labeled nucleic acid probe and comparing the expression of BMX with a second normal tissue type or a from an unaffected individual, wherein a difference in expression indicates that the first individual (the supposed affected one) is undergoing angiogenesis. The claims are also drawn to a method comprising determining the level of an angiogenesis modulating protein (AMP), wherein the AMP is encoded by the BMX gene, and wherein level is determined by a labeled nucleic acid probe. Tamagnone *et al* disclose a method of determining the expression of BMX in HUVEC and compared into to tissues that lack the expression of BMX. Tamagnone *et al* also compared the expression of BMX protein in HUVEC to tissue lacking the expression of BMX. Therefore, the method claimed is anticipated because the basic method of determining the levels of BMX have already been taught.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Christopher Yaen
Art Unit 1642
May 19, 2003

ALI R. SALIMI
PRIMARY EXAMINER